

TRIP REPORT—MINSK, 28 MARCH – 2 APRIL, 1999 – J. ROBBINS

This trip was designed to concentrate on clinical matters and was conducted by Robert McConnell and myself. Drs. Brill and Beebe had planned to participate but had to cancel. Everett Mincey, another potential participant, failed to materialize. We found this small-team approach to be very satisfactory and productive in achieving our limited goals, realizing of course that important areas were left untouched. In particular, we did not discuss cohort formation, which would have been covered by Dr. Beebe, or laboratory activities, and we did not have time to focus on mobile team operation.

Physical set up

Most of our time was spent in the new screening center of the newly located Dispensary of the Institute of Radiation Medicine and Endocrinology (IRME). The Dispensary is reachable by Metro but the walk from the station is rather long. We used Ninna Litvinova's office for our meetings. The dreadful mud bath installations occupying the area on our last visit in October 1998 have been completely removed, several offices and the interview room are completed and are suitable, the laboratory space is completed and Petrenko had already installed several freezers and began moving his equipment during the week. The corridor was still under construction, and Dr. Rzhetski proposes that the end portion could be used for the DCC. It is not a large space but may be satisfactory and would, of course, improve communication and operation. Blood drawing and ultrasound are currently being done upstairs in the dispensary space.

Dr. Danilova told us that Rzhetski will provide her with several rooms close to the screening center for her to use as an office and for teaching. This will permit her to be more closely involved with the screening operations.

We visited the DCC and epidemiology office, which occupies about half of a floor in an office building some distance from the screening center. It is conveniently located near a Metro station. The large space is divided by temporary partitions and stacked boxes. Dr. Ostapenko, the new director of IRME, has an office not too far from the DCC but we did not see it.

Staff with whom we interacted

Essentially all of our meetings were with Litvinova and Olga Polyanskaya. Rzhetski kept in touch with what we were doing. Larissa Danilova was out of town the first day but then took part on several occasions. Vitaly Klevich, the ultrasonographer, was available when needed, and Valentina Drozd participated a few times. Boris helped with transportation and other arrangements, and did some interpretation (not nearly as well as Olga). Arthur Kuvshinnikov was present on several occasions, is obviously being used as needed by the team, and seemed happy and satisfied. Serge Melnov was supposed to telephone me but never did. Yuri Demidchik came to discuss possible arrangements for his visit to thyroid surgical centers in the USA, funded by the Thyroid Foundation of America. He still wishes to come but has had difficulty in obtaining permission from his chief. He again promised to let us know soon.

We attended the beginning of the weekly staff meeting to report our findings and impressions. We said that our visit was useful and that we were impressed with the progress in entering screening records into the computer data base. We also said that we were particularly impressed with the beneficial effect that Polyanskaya's addition to the staff had had on the progress of the work since our last visit in October 1998. This was

due in large part to her ability to interrelate the various arms of the project as related to her quality assurance activities. All principal members of the BY team were in attendance, including Ostapenko. Unfortunately, we were unable to meet with him except to exchange pleasantries. He was supposed to attend a dinner party at Polyanskaya's apartment at the end of the week but cancelled at the last moment because his wife's train returning from Mogilev was delayed.

At the symposium on thyroid and parathyroid tumors in Pisa, Italy, which I attended just before going to Minsk, several members of the BY and UA project teams were present. They included Tronko, Drozd (who had several posters on the program), Eu.Dimidchik, Epstein, and several junior colleagues. The principals were there to attend an EU meeting with Dr. Pinchera.

Abstract for the European Thyroid Association (ETA) meeting, Milan, Aug-Sept. 1999

About one third of our time in Minsk was spent on preparing the abstract. This was very useful, however, because it enabled us to review data on goiters and thyroid nodules during 2 years of screening. The earlier summary presented in the Quarterly Report was in error because Polyanskaya had discovered that some records in the data base had been entered more than once.

At this time, all available data on all 3649 subjects screened during 26 months of the project (January 1997 to March 1999) have been entered in the computer data base. This includes all palpation and ultrasound exams, some laboratory data, and preliminary screening summaries. Of the total screened, 1312 were done in 1997. Most of the entries into the data base were made during the last quarter of 1998, and entries are now made within about 2 days after screening.

Our review permitted an apparently accurate assessment of the number of nodular and diffuse goiters, benign nodules and cancers. Thyroid size was based entirely on ultrasound measurements. The data are summarized in the attached abstract. There were 134 nodular goiters, 104 of which were solitary nodules, and 41 thyroid cancers, all papillary carcinoma, 13 of which were newly discovered. There were 140 diffuse goiters (>150% above normal thyroid volume). No laboratory-based data are included because these are incomplete and have not been validated.

The Belarusian authorship was decided by Polyanskaya and Danilova.. The first (presenting) author is Polyanskaya, followed by all who were principals of the BY team during the reported screening period in alphabetical order, and then by 4 members of the USA team who had helped with the abstract, also in alphabetical order.

The abstract was completed and sent by express mail on Friday, April 2. The required registration form and payment by the presenting author was completed with payment through my personal credit card. Polyanskaya obtained assurance from Ostapenko that he would obtain funds for her registration but there was no time to accomplish this. The package also included my own registration form and payment and a letter to Paolo Beck-Peccoz, organizer of the meeting, explaining the situation. Danilova, who intends to attend the meeting under other auspices, offered to share her hotel room with Polyanskaya.

Review of screening records

Paper records of all nodule and goiter cases were set aside in Litvinova's office, but we were able to review only nine of them because we had extensive discussions of the items of concern and the questions that were raised. Both Litvinova and Polyanskaya indicated that their questions were adequately answered and that we had settled their

concerns. The cases reviewed included thyroid cancers, benign thyroid nodules and possible thyroiditis.

Completion of the endocrine history, palpation and ultrasound forms were found to be satisfactory. The hospitalization forms were not adequately completed. The reports from Aksakovtchina contained minimal information, but Polyanskaya had succeeded in arranging to receive the complete hospital data printouts in the most recent cases. (We did not determine whether this would be done for the backlog of cases.)

The surgery reports were also inadequate, mainly because they did not contain the gross surgical findings, only giving the TNM classification. In several cases the TNM recorded by the surgeon did not match that in the pathology report: the former were listed as T2 where the latter were T4. (T4 signifies invasion beyond the thyroid capsule.) This apparently was because the pathologist (Cherstvoy) based his TNM classification on microscopic invasion and did not have access to the gross anatomy of the specimen. There either was no agreement between Cherstvoy and Siderov, the pathologist in the surgical oncology department, or more likely, the surgery report reflected only gross invasion of the tumor. In earlier conversations we had been told that both pathology groups exchanged information about the gross anatomical findings.

Although the TNM classification does not affect whether the diagnosis of malignancy is correct or not, it is important that this problem in classification be resolved in the near future. We were told that Narovnya, the senior pathologist in Cherstvoy's department, had turned down an offer to move to surgical oncology and that the problem had been brought to the attention of the minister of health. We were advised not to raise the issue when we reported to the weekly staff meeting. This leads us to recommend that review of the findings by a committee of expert pathologists be arranged very soon. The committee should have access to the surgeons' reports and to the gross and microscopic anatomy findings in both pathology departments.

Treatment of patients with nodules not referred for surgery

All patients found to have a thyroid nodule that is not referred for surgery are recommended to receive thyroxine, 100 mcg per day for 3 months, alternating with no treatment for one month. In some cases additional treatment with potassium iodide, 150 mcg per day, is recommended. These medications are expensive and we obtained the impression that treatment is quite irregular. Although we agreed that the issue of treatment of these patients is a matter for the local health authorities to decide, we urged that patients in the BelAm cohort should receive identical treatment, as determined by fixed criteria, in order to avoid bias. This matter should receive continuing attention and monitoring.

Problems discussed

TNM classification of thyroid cancer. This has been described above.

Treatment of non-operated thyroid nodules. This has been described above.

Goiter size. Although this is based on ultrasound measurement, it must be recognized that the definition of "normal" for Belarus is based on measurements that have been made previously in a non-exposed region of the country but not necessarily one that is not deficient in iodine. This will need further attention and verification that measurement in regions without iodine deficiency have been used. It may even be necessary to do new measurements to establish the normal range for different age groups.

Definition of multinodular goiter. It was agreed that this should include any thyroid that contains more than one nodule. Although this may be satisfactory for data entry at this point, I believe that we will ultimately need to distinguish between grossly multinodular goiters and those glands that contain only 2 or 3 discrete nodules. Presumably this could be done when data are summarized, but it would be better if a way could be found to have three classes of nodular goiter: solitary nodule, 2 to 3 or 4 discrete nodules, more than 3 or 4 nodules. We did not succeed in this but perhaps should try again. The issue is important because one of the strengths of our study is to determine the risk for development of benign thyroid nodules as well as thyroid cancer.

Resolution of differences between palpation findings by the two examiners. As in the original plan, the endocrinologist and the sonographer each palpate the thyroid. If they are unable to resolve a difference, the plan calls for a third exam by a senior endocrinologist, but we were told that they do not have the staff to do this. Instead, the senior endocrinologist who completes the Screening Summary Form (Litvinova) resolves the issue of palpability. Often she is the palpating endocrinologist and I suspect that she may give priority to the endocrinologist's opinion. We agreed that the endocrinologist's opinion, after reexamining the subject with knowledge of the ultrasound result, should be the basis for the summary report. This means that a nodule that is palpable but not detected by ultrasound would be confirmed by reexamination by one endocrinologist. Conversely, a defect seen by ultrasound but not palpated would be confirmed in the same way. This issue should be revisited in the future by asking to review records where there have been discrepancies.

Definition of autoimmune thyroiditis. Uncertainty about this question has prevented entry of this diagnosis into the data base. In addition, the results of antithyroid antibody analyses are incomplete. There have been about 50 cases with antiTPO >100, about a third of whom have increased antiTG. This is in ~1333 screened individuals, or ~4% of those tested, which is not unreasonable. We discussed the issues raised in Dan Fink's report about the antiTPO tests, and this needs further attention. We agreed, however, that a coding system was needed to identify the criteria on which the diagnosis of thyroiditis is based. This was resolved as follows: subclassifications under ICD 245.2 (chronic lymphocytic thyroiditis) would be .21=positive antibodies only, .22=positive FNA only, .23=positive ultrasound only, .24=increased TSH and positive antibodies, .25= palpable abnormality and positive antibodies. (Note: See McConnell's report for possible discrepancies. His list should be more accurate.)

It was also agreed that the epidemiologist will receive only the ICD245.2 classification, not the subclasses. Furthermore, the diagnosis would be made only after reexamination of the subject after an interval of about 6 months.

Selection for aspiration biopsy (FNA) and surgery. Several recent referrals to Aksakovtchina for tests prior to surgery have been completed in one week but Polyanskaya and Litvinova are still concerned that patients who are returned for surgery may not report to oncology and thus will be inadequately treated or even lost to follow up. Polyanskaya is opposed to referrals to Aksakovtchina for tests the results of which will not be shared with the BelAm project. She also believes that patients resent deferral of needed surgery when the tests are optional with respect to their treatment. Obviously, the patient's informed consent is required. Furthermore, she says that surgery needs to be

rescheduled, which can take as long as a month. This should be solvable by pre-scheduling the surgery date and escorting the patient to the oncology department. We reviewed one case in whom the screening center diagnosis was benign hyperplasia, who was then referred for surgery by the Aksokovtchina clinic and had a post surgical diagnosis of cancer, so there are mixed signals on this question. It deserves further attention by reviewing the records of pertinent cases.

Sharing data with Epidemiology. We were told that Epidemiology wants to receive all of the clinical data on each subject but Polyanskaya maintains that they should receive only the final diagnosis. We agreed that the latter procedure was appropriate and would avoid potential misunderstanding and confusion.

Ultrasound data management. Ultrasound results are being recorded on MOD but have not been transferred to CD-ROM. We were told about a new recording system that has been adopted by the Dispensary and we visited the DCC for a demonstration of the software. This apparently has been set up by Kuvshinnikov, and he says that he has sent information about it to Randy Brill but has received no response. The advantage of this new method is that provides a direct interface between the ultrasound examination and CD-ROM. The software cost is about \$1500 for the first installation, which is reduced for secondary installations. The claim is that its use would result in cost saving since new MOD setups would not be required for each new ultrasound location. We urged that complete technical information and cost accounting be sent to Brill and Masnyck for their decision as to whether to adopt this new procedure.

ICD codes. The lists prepared by McConnell together with my comments to him were left with Polyanskaya for her study and later discussion with us during the June visit.

Rescreening. We were told that about a third of the subjects have been rescreened after a one year interval and that many subjects do not respond to recall requests. We did not obtain actual data about this problem nor any explanations.

Improving acceptance of screening. Rzhetski proposed that the screening of young people could be improved by doing it during summer vacation when they are attending summer camps in the Minsk region.

Forms. Polyanskaya suggested several revisions which we approved. The Final Screening Summary will no longer include surgery and pathology data. These data go separately into the computer data base. Other changes were minor.

Recommendations.

- A committee for expert pathology review should be convened in the near future by Masnyk and Stezhko.
- Cytologists' agreement on nomenclature of benign neoplasms is needed. (The cytologist visited us to discuss the material she received from Ellen Greenbaum. Her questions about malignant neoplasms were resolved but we could not satisfy her on the nomenclature for benign neoplasms.)
- A system for recalling subjects for screening is needed, including an automated notice mechanism for subject and physician.

- Treatment of nodules that are not submitted to surgical excision, and post operative management after excision, should be standardized.
- As requested by Polyanskaya, Herman Mitchell should review the last quarterly report and advise her on how to conduct computer searches for errors in the data base and how to automate detection of missed appointments.